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ISSCR Guidelines for Stem Cell Research and Clinical Translation: The 2021 update

Robin Lovell-Badge,[1,*] Eric Anthony,[2] Roger A. Barker,[3] Tania Bubela,[4] Ali H. Brivanlou,[5] Melissa Carpenter,[6] R. Alta Charo,[7] Amander Clark,[8] Ellen Clayton,[9] Yali Cong,[10] George Q. Daley,[11] Jianping Fu,[12] Misao Fujita,[13] Andy Greenfield,[14] Steve A. Goldman,[15,16] Lori Hill,[17] Insoo Hyun,[11,18] Rosario Isasi,[19] Jeffrey Kahn,[20] Kazuto Kato,[21] Jin-Soo Kim,[22] Jonathan Kimmelman,[23] Jürgen A. Knoblich,[24] Debra Mathews,[20] Nuria Montserrat,[25] Jack Mosher,[2] Megan Munsie,[26] Hiromitsu Nakauchi,[27,28] Luigi Naldini,[29] Gail Naughton,[30] Kathy Niakan,[1,31] Ubaka Ogbogu,[32] Roger Pedersen,[27] Nicolas Rivron,[24] Heather Rooke,[33] Janet Rossant,[34] Jeff Round,[35] Mitinori Saitou,[13] Douglas Sipp,[36,37] Julie Steffann,[38] Jeremy Sugarman,[20] Azim Surani,[39] Jun Takahashi,[13] Fuchou Tang,[10] Leigh Turner,[40] Patricia J. Zettler,[41] and Xiaomei Zhai[42]

[1]Francis Crick Institute, London, UK
[2]International Society for Stem Cell Research, Skokie, IL, USA
[3]Cambridge Center for Brain Repair and WT-MRC Stem Cell Institute, Cambridge, UK
[4]Simon Fraser University, Burnaby, BC, Canada
[5]The Rockefeller University, New York, NY, USA
[6]ElevateBio/Carpenter Group Consulting, Waltham, MA, USA
[7]University of Wisconsin-Madison, Madison, WI, USA
[8]University of California, Los Angeles, Los Angeles, CA, USA
[9]Vanderbilt University, Nashville, TN, USA
[10]Peking University, Beijing, China
[11]Harvard Medical School, Boston, MA, USA
[12]University of Michigan, Ann Arbor, MI USA
[13]Kyoto University, Kyoto, Japan
[14]MRC Harwell Institute, Oxfordshire, UK
[15]University of Rochester Medical Center, Rochester, NY, USA
[16]University of Copenhagen, Copenhagen, Denmark
[17]MD Anderson, Houston, TX, USA
[18]Case Western Reserve University School of Medicine, Cleveland, OH, USA
[19]University of Miami, Coral Gables, FL, USA
[20]Berman Institute of Bioethics, Johns Hopkins University, Baltimore, MD, USA
[21]Osaka University, Suita, Japan
[22]Seoul National University, Seoul, Korea
[23]McGill University, Montreal, QC, Canada
[24]IMBA-Institute of Molecular Biotechnology, Vienna, Austria
[25]Institute for Bioengineering of Catalonia (IBEC), Barcelona, Spain
[26]University of Melbourne, Melbourne, VIC, Australia
[27]Stanford University, Stanford, CA, USA
[28]University of Tokyo, Tokyo, Japan
[29]Università Vita-Salute San Raffaele, Milan, Italy
[30]Histogen, San Diego, CA, USA
[31]Centre for Trophoblast Research, University of Cambridge, Cambridge, UK
[32]University of Alberta, Edmonton, AB, Canada
[33]Broad Institute, Cambridge, MA, USA
[34]Gairdner Foundation/SickKids, Toronto, ON, Canada
[35]Institute of Health Economics, Edmonton, AB, Canada
[36]RIKEN Center for Developmental Biology, Wako, Japan
[37]Keio University School of Medicine, Tokyo, Japan
[38]Université Paris Descartes, Paris, France
[39]Gurdon Institute, University of Cambridge, Cambridge, UK
[40]University of Minnesota, Minneapolis, MN, USA
[41]Ohio State University, Columbus, OH, USA
[42]Peking Union Medical College, Beijing, China
*Correspondence: robin.lovell-badge@crick.ac.uk
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SUMMARY

The International Society for Stem Cell Research has updated its Guidelines for Stem Cell Research and Clinical Translation in order to address advances in stem cell science and other relevant fields, together with the associated ethical, social, and policy issues that have arisen since the last update in 2016. While growing to encompass the evolving science, clinical applications of stem cells, and the increasingly complex implications of stem cell research for society, the basic principles underlying the Guidelines remain unchanged, and they will continue to serve as the standard for the field and as a resource for scientists, regulators, funders, physicians,

and members of the public, including patients. A summary of the key updates and issues is presented here.

OVERVIEW OF THE GUIDELINES—EVOLVING WITH THE SCIENCE

With any area of research, especially when it relates to humans and involves issues that may be considered ethically contentious, it is important to ensure it is subject to appropriate review and oversight. The stem cell field is one such area, and while some countries have relevant laws and policies governing how research and clinical applications are conducted, many jurisdictions around the world do not or they have legislation with substantial gaps and ambiguities. Given this, carefully constructed guidelines can play a critical role for scientists and clinicians conducting research and treating patients; for the public who may have hopes for or concerns about the research, may be funding it, and may become recipients of any treatments that result from it; and for governments that may have other more pressing demands on their capacity to develop laws and policies and establish institutions to support them.

The International Society for Stem Cell Research (ISSCR) was founded in 2002 and rapidly grew to become the preeminent global, science-based organization dedicated to all aspects of stem cell research and its clinical translation. In addition to its role as a member-based organization to promote scientific discourse and the sharing of data, early on the Society decided it should undertake the responsibility for developing guidelines to encourage high standards in practical and ethical aspects of relevant research and its applications.

The first ISSCR Guidelines, published in 2006, had a major focus on human embryonic stem cells (hESCs), which had first been derived only 8 years earlier (Daley et al., 2007). By 2006, numerous hESC lines were being used by researchers in many countries, with substantial variation in both methodology and in the way their derivation and use was regulated. The 2006 Guidelines built upon the experience with earlier, more local efforts, reflecting underlying ethical principles for research, and proposed that institutions should establish stem cell research oversight (SCRO) committees. This was important to give regulators and the public confidence that hESC lines were being derived and used both sensibly and with sensitivity.

In 2008, the ISSCR issued Guidelines focused on the clinical translation of stem cell therapies, essential if these were to realize their potential for regenerative medicine. Then, in 2016, the ISSCR updated and combined the previous two Guidelines, incorporated research and uses of induced pluripotent stem (iPS) cells, articulated ethical principles for stem cell research (such as integrity of the research enterprise, respect for patients and research subjects, and social and distributive justice), and expanded the purview to include research involving human embryos (Daley et al., 2016; Hyun et al., 2008). At the time, the latter was justified by the following: "Acknowledging that stem cell researchers engage in many forms of human embryo research that do not explicitly involve derivation or use of hESC lines, the guidelines broaden the scope of specialized review beyond the SCRO function to encompass all forms of human embryo research. The … human embryo research … may not explicitly pertain to stem cells or stem cell lines, such as single cell analyses, genome modification, and embryo chimerism" (Daley et al., 2016). The 2016 Guidelines also proposed that, depending on the nature of the experiments to be conducted, review should entail a renamed "Embryo Research Oversight (EMRO)" process, signaling this wider remit.

Over the last 5 years, there have been several key developments in the science related to the biology of stem cells and human embryos and to their potential and actual uses, including the application of genome editing, as well as an increase in examples of appropriate and inappropriate clinical applications. The pace, extent, and potential importance of the new developments, and how they affect one other, have demanded a substantial rewrite and expansion of many sections of the ISSCR Guidelines, a two-year collaboration with international experts and respected leaders in areas of stem cell science, ethics, and law (Box 1). Key advances that the new 2021 Guidelines cover include the following: the culture of human embryos and stem cell-derived models of embryo development, both embryo-like entities and specific organ-like structures (organoids); chimeras; *in vitro* gametogenesis from cells; mitochondrial replacement techniques; somatic and germline genome editing; enhanced guidance for procurement of stem cell lines; and more robust clinical translation guidance (https://www.isscr.org/guidelines, see also "Summary of recommendations from the ISSCR Guidelines for Stem Cell Research and Clinical Translation" and "Summary of significant changes in the 2021 ISSCR Guidelines for Stem Cell Research and Clinical Translation" in the supplemental information). These new developments justify even more the inclusion of embryo research within the Guidelines, especially as ESCs or iPSCs can provide both a test of methodology before moving to embryos and ESCs can provide subsequent tests of safety and efficacy. Moreover, while the 2021 ISSCR Guidelines have evolved most clearly with respect to the underlying science, it also reflects evolving attitudes to what might be permissible, both in research and possible clinical applications, as well as to the importance of certain values,

Box 1. The process

The ISSCR Board established the Guidelines Revision Task Force, comprising 45 members (the authors of this article), in June 2019. This was carried out in consultation with the Chair, who had been identified earlier, and involved discussions with other key individuals to help ensure breadth and balance. It was felt important to ensure that the new Guidelines be developed by drawing on a wide range of perspectives, discplines, and backgrounds and that it was not just informed by science but by ethical, legal, regulatory, clinical, and commercial viewpoints.

OVERVIEW OF STRUCTURE

A steering committee comprising ten members, each with substantial experience in aspects of stem cell research and in formulating guidelines, was established. The Committee included the Chair of the task force responsible for the previous revision of the ISSCR Guidelines in 2016. The steering committee oversaw the process via frequent online meetings and one in-person meeting in San Francisco in February 2020. The latter was an important occasion to establish the topics that would provide the focus of many of the revisions as well as providing a direction of travel for some of these.

The task force was also supported throughout by members of the ISSCR Policy and Outreach Teams, notably by Eric Anthony, Jack Mosher, and Glori Rosenson, who deserve much of the credit for the revised Guidelines.

The task force was divided into four working groups, each chaired by two steering committee members, with globally diverse expertise, and focused in four key areas:

(1) Genome editing and MRT
(2) Embryos, embryo models and gametogenesis research
(3) Organoid and chimera research
(4) Regulatory, pricing, and access issues

The working groups and steering committee met often over the course of 15 months to draft and revise the Guidelines. An early draft of the revised Guidelines was reviewed in May 2020 by the ISSCR Ethics, Public Policy, Clinical Translation, and Industry committees and then by the ISSCR Board in June 2020. This led to a number of revisions and updates. The next draft was subject to extensive and international external peer review during September and October 2020, which resulted in additional modifications. Based on this version, the main revisions being made in the Guidelines were then presented to ISSCR members in four separate briefings during November 2020. Further revisions and updates were then incorporated before a more complete draft was given to the ISSCR Board, gaining their approval in December 2020. As the final version was being prepared, between then and now, some additional changes and updates were made, but in each case the wording was assessed by both the relevant working group and the steering committee.

such as those of openness, transparency, fairness, and equitable access to new therapies. This has also necessitated a fresh look at mechanisms ensuring appropriate review and oversight of research and clinical applications, where the Guidelines now place greater emphasis on the considerations that should be addressed rather than on specific committees.

SCIENTIFIC AND ETHICAL REVIEW

Robust mechanisms of review and oversight are essential to develop and maintain confidence in research and its applications. These help to ensure best practice with respect to the science and ethics, including obtaining informed consent from donors and patients. The updated Guidelines maintain rigorous independent review for human stem cell and embryo research, and for related research activities, but provide additional clarity, criteria, and practical guidance for its oversight. To emphasize both the purpose of the review and how it must be capable of evaluating the unique aspects of the science and the associated ethical issues of the research, along with broader concerns, the revised Guidelines now refer to it simply as a "specialized scientific and ethics oversight process." They indicate that the review can take place at the institutional, local, regional, or national level but encourage mechanisms to ensure consistency wherever possible. Moreover, although the Guidelines no longer recommend any specific named committee or process, they propose that it should be conducted by an established body, including an EMRO, ESCRO, SCRO, or other committee, as long as this includes the relevant expertise appropriate for the topic being reviewed, as well as having generalists and lay members.

Box 2. Categories of research

A brief summary of the categories of research from the 2021 ISSCR Guidelines for Stem Cell Research and Clinical Translation. For more detailed guidance, please see https//www.isscr.org/guidelines.

Category 1A—Exempt from review by a specialized oversight process

- Most *in vitro* pluripotent stem cell research
- Most *in vitro* organoid research
- Transfer of human stem cells into postnatal animal hosts

Category 1B—Reportable but not typically reviewed by a specialized oversight process

- Non-integrated stem cell-based embryo models
- *In vitro* culture of chimeric embryos (human cells into non-human embryos)
- *In vitro* gametogenesis without fertilization or generation of embryos

Category 2—Reviewed by a specialized oversight process

- Procurement of embryos, or gametes for the creation of embryos, for *in vitro* research
- Derivation of cell lines from human embryos
- Genetic alteration of embryos or gametes
- *In vitro* culture of human embryos for research until the formation of the primitive streak or 14 days from fertilization, whichever comes first
- Human cells transplanted into nonhuman embryos that are gestated in a non-human uterus
- Integrated stem cell-based embryo models
- Transferring human embryos following MRTs into a human uterus

Category 3A—Not allowed: Currently unsafe

- Heritable genome editing for reproductive purposes
- Transferring mtDNA-modified (not including MRTs) embryos into a uterus
- Using gametes differentiated from human stem cells for reproduction

Category 3B—Not allowed: Lacks compelling scientific rationale and/or is ethically concerning

- Gestating human stem cell-based embryo models
- Human reproductive cloning
- Breeding human-animal chimeras where there may be human germ cells.
- Transferring human-animal chimeric embryo(s) to a human or non-human primate uterus
- Transferring human embryo(s), irrespective of origins, to an animal uterus

As in previous iterations, the review process proposes several categories covering both research and its applications, but to accommodate advances in science and changing views, the Guidelines now subdivide some of these (see also Box 2).

Category 1, which previously captured research exempt from review, now has two subcategories: 1a and 1b.

1A includes research determined to be exempt from a specialized scientific and ethics oversight process after being assessed by the appropriate existing mandates and committees for laboratory research. This includes the routine culture of pluripotent stem cell lines, the reprogramming of human somatic cells, and research on stem cell culture systems that model specific stages of development or specific anatomic structures including organoids. Of course, as with all research actively involving the acquisition of human cells or tissues, appropriate consent must first be obtained from the donor or their legal representative.

1B is a new sub-category that includes types of research that need to be reported to the entity responsible for the specialized scientific and ethics oversight process, but at the discretion of this entity and subject to regulations and policies in the relevant jurisdiction, the research need not normally be subject to further or ongoing review. This covers projects that may be of no public concern in themselves but that have the potential to lead to work that might, such as *in vitro* chimeric embryo research and *in vitro* gametogenesis where there is no intent to generate a human embryo.

The principles covering review under Category 2 remain the same; however, this now includes additional types of research. It is research under this category that will clearly give the majority of work for the specialized scientific and ethics oversight process (see Box 2). It includes research that the process might conclude is permissible, perhaps with conditions applied, and as long as it also complies with regulations and policies in the relevant jurisdiction.

Category 3, as before, is concerned with types of research that are prohibited. However, it has now been revised and subdivided into two categories to make a distinction between the reasons for prohibition.

3A includes research activities currently not permitted because the approaches are not yet considered safe enough and/or raise ethical issues that are unresolved. Examples include research on human germline genome editing, mitochondrial genome editing, and the use of human gametes differentiated from human stem cells for fertilization and human reproduction.

3B includes prohibited research activities that should not be pursued because of broad international consensus that such experiments lack a compelling scientific rationale and are widely considered to be unethical. This category includes human reproductive cloning, breeding chimeras that may contain human gametes, and transfer of human embryos to an animal uterus, among other lines of research.

NOTABLE NEW GUIDANCE

Embryo culture and embryo models

Two papers were published in 2016, around the time the previous version of the Guidelines was published, showing that it was possible to culture intact preimplantation human embryos up to the equivalent of 13-day post-implantation embryos, i.e., shortly before gastrulation, which begins around 14 days in humans (Deglincerti et al., 2016; Shahbazi et al., 2016). The methods were based on those developed about 2 years earlier for mouse embryos, with evidence that these could undergo gastrulation. It has been possible to culture macaque embryos up to about 20 days, well beyond the 14-day equivalent and gastrulation in human embryos (Ma et al., 2019; Niu et al., 2019). This has not been done with human embryos because of the "14-day rule" that has been adopted in some guidelines, including those from the ISSCR, and enshrined in law in several countries, such as in the UK since 1990. There is now building pressure to extend or even abolish this limit in order to permit research into very important stages of human embryo development, about which we know little, but where many cases of miscarriage or birth defects are likely to have their origins (Hyun et al., 2021; McCully, 2021; Williams and Johnson, 2020). Other reasons for extending the culture period include (1) to provide control material against which to validate stem cell-based embryo models (see below), which, if successful, would reduce the future need to carry out some types of research directly with human embryos, and (2) to enable more thorough analysis of safety and efficacy of a wide range of methods either currently employed in IVF or that could be introduced, notably mitochondrial replacement techniques, heritable human genome editing, and *in vitro*-derived gametes (see below) (Clark et al., 2021).

Consequently, the *in vitro* culture of any intact human preimplantation embryo beyond 14 days or formation of the primitive streak (whichever occurs first) is now removed from Category 3. Instead, all research involving culture of intact human embryos is subject to Category 2 review, but balancing the potential value of this research with the ethical and societal concerns raised by it and taking into account the social responsibility to be transparent throughout the process, the guidelines recommend that, before a committee responsible for the specialized scientific and ethics review process may even consider applications for human embryo research beyond formation of the primitive streak or 14 days, national academies of science, academic societies, funders, and regulators should lead public conversations on the scientific significance as well as the societal, moral, ethical, and policy issues raised by allowing such research (Recommendation 2.2.2.1, Matthews et al., 2021). This public dialog should help provide guidance on what types of experiments might prove permissible.

One of the guiding principles of the review process with respect to human embryos is that there should be no valid (and existing) alternative way of obtaining the same information. This leads to the topic of embryo models. In parallel to the development of embryo culture systems, stem cell-based embryo models have rapidly advanced since the 2016 Guidelines and two distinct types are now recognized by the new Guidelines.

The first is non-integrated models (Category 1B). These experimentally recapitulate some, but not all, aspects of the early postimplantation embryo and would include gastruloids. These lack extra-embryonic cells types and may have only a partial anterior-posterior embryonic axis and would therefore have no reasonable expectation of achieving substantial development *in vitro* or *in vivo* if any attempt was made to transfer them to a human or animal uterus. These were previously part of Category 2 when no distinction was made between non-integrated and integrated models.

The second is integrated models (Category 2). These models, which include "blastoids" derived entirely from stem cell lines, contain relevant embryonic and extra-embryonic cell types and could potentially achieve the complexity by which they might realistically undergo further integrated development if cultured for additional time in appropriate conditions or, theoretically, if transferred to a uterus. After review by the specialized scientific and ethics oversight process, and if permission is given, these could be maintained in culture for the minimum time necessary to achieve the specific scientific objectives. Any absolute time limit, such as 14 days, would not make sense, in part because these entities would already have had an extended period in culture as stem cells, but also because they are not bona fide embryos. Despite what

may eventually prove to be a close resemblance to the latter, they are very unlikely to possess typical epigenetic marks and may miss specific cell states required for viable embryogenesis. In addition, because they are derived from stem cell lines, this allows generation of many genetically identical blastoids, which has experimental advantages; but this would be another potential route to "human reproductive cloning," which is not permissible for any reason. Thus, transfer to a human or animal uterus is not permitted (Category 3B). Nevertheless, such models might well reduce the need for genuine human embryos in some types of research. More detailed discussion of embryo culture and embryo models can be found in the white paper by Clark et al. elsewhere in this issue (Clark et al., 2021).

In vitro-derived gametes

While not yet achieved, there has been notable progress in research aimed at generating functional gametes from stem cells, either entirely *in vitro* or after a combination of *in vitro* culture followed by incorporation into gonads or gonadal-like structures *in vivo*. This progress is most pronounced with animal models, notably mice, where *in vitro*-derived sperm or oocytes have been obtained via directed differentiation of pluripotent stem cells followed by co-culture with testicular or ovarian cells, respectively, or in a range of mammals from the mouse to macaques, where spermatogonial stem cells can be cultured, genetically manipulated, and then introduced into the testis to undergo spermatogenesis. Moreover, at least a proportion of gametes derived with these protocols have been shown to be capable of giving rise to zygotes after fertilization and then to embryos and live born animals. There are many reasons for trying to achieve this in humans, notably, the following: (1) as a way to research and understand human germ cell and gamete development, which has been very difficult to study; (2) as a means to restore fertility, e.g., after cancer radiotherapy or chemotherapy; (3) to provide a supply of gametes, notably oocytes, for a wide range of studies on early embryos, reducing the need for gamete donors; and (4) to provide a route to heritable human genome editing (see below). The revised Guidelines hold that research conducted *in vitro* involving the derivation of human sperm or oocytes can proceed without review by a specialized oversight process, as long as no attempt is made to fertilize them or otherwise create embryos. However, because of the likely interest and concern from both the public and regulators, this research has been placed in Category 1B. If, however, the research entails testing gametes derived after any period of *in vitro* culture by fertilization and/or the creation of embryos, this must be subject to review, approval, and ongoing monitoring, as appropriate, through a specialized oversight process capable of evaluating the unique aspects of the science and the associated ethical issues. This latter research is therefore firmly in Category 2.

Organoids

Methods to derive and culture specific cell types, tissues, and organoids from stem cells have also improved since 2016, with a greatly expanded repertoire of sometimes quite sophisticated structures now being studied. Most of these raise few ethical concerns. However, extensive coverage of the topic by the media prompted discussions during the process of revising the Guidelines whether work using central nervous system (CNS) organoids warranted review through the specialized oversight process. These discussions included the question of whether CNS organoids may achieve consciousness or perceive pain. However, at this time, there is no biological evidence to support such concerns. Both require a level of complexity and maturity and connections with relevant sensory systems that are not achieved in any current culture system. Consequently, all organoid research is currently in Category 1A. Nevertheless, the ISSCR and future Guidelines update committees should review this topic as science advances and additional information becomes available (National Academies of Sciences, Engineering, and Medicine, 2021).

Human-animal chimeras

There are many reasons why it can be useful to generate animals containing human cells or tissues. These notably include assaying the potential of human stem cells in an *in vivo* situation, creating better animal models for studying human disorders and ways of treating these, and even perhaps the generation of organs and tissues for transplantation. This is a complex area where concerns vary according to type and stage of non-human animal used as recipient/host and the specifics of the human cells, notably whether they have a broad or narrow potential (which may only be discovered on carrying out the experiments). Additional methods, such as "blastocyst complementation" can also be used, at least in theory, to allow human cells introduced into early embryos to completely replace a specific tissue or even, perhaps, to confine their likely contribution to only this tissue in the resulting animal. As with other methods outlined in this article, there have been significant advances made over the last 5 years in making and analyzing such chimeras, and these are very likely to continue apace.

Relevant areas of potential research fall into almost all of the review categories. If the experiment involves the transfer of a few stem cells into a postnatal animal, then this would not require any special review outside that provided for animal research generally; i.e., it would be Category 1A. Chimeric embryo research in which pluripotent human stem cells are transferred into mammalian non-human embryos and cultured *in vitro* would be Category 1B. This is a new requirement making these experiments reportable,

more because they might be of public interest rather than their raising unique ethical concerns. A recent example of this involved introducing "expanded potential" human pluripotent stem cells into macaque blastocysts that were then cultured to primitive streak stages, where they showed a modest contribution (Tan et al., 2021). If such experiments involved the transfer of the embryos into the uterus of a non-human animal, this would fall under Category 2 because it would clearly demand consideration by the special review and oversight process (although this would exclude transfer into greater and lesser apes, which is prohibited). A particular concern arises if there were a substantial contribution of human cells to the CNS of the animal. It will be difficult to predict how brain size and connections to animal sensory and motor systems will affect phenotypes. Therefore, such experiments should proceed in a careful stepwise manner, with review at critical stages, paying particular attention to behavior and animal welfare issues if any of the chimeras are brought to term (National Academies of Sciences, Engineering, and Medicine, 2021). Finally, transfer of such chimeras into a human uterus or breeding chimeric animals where there is a chance they have human gametes are prohibited and clearly fall into Category 3B. For more about this topic and the discussions around it, please see Hyun et al. (2021) in this issue.

Mitochondrial replacement techniques

Mitochondrial replacement techniques (MRTs) involve the transfer of nuclear genetic material, notably the meiotic spindle with chromosomes attached before fertilization or both the maternal and paternal pronuclei at the zygote stage after fertilization, into an enucleated oocyte or zygote at the equivalent stages. (A third method, polar body transfer, might also be feasible, but published data on this are limited.) This has the effect of swapping the cytoplasm, which contains the mitochondria with their DNA (mtDNA), in order to effectively replace pathogenic mtDNA's causing serious disease with normal mtDNA. This should allow a woman (mitochondria are only inherited via the mother) at risk of having an affected child to have a genetically related child free from mitochondrial disease. The child would have contributions as normal from the mother's nuclear DNA as well as that from the father, but mtDNA from the oocyte donor. To date, the the UK is the only country to actively permit in law the use of MRTs specifically to avoid serious mitochondrial disease. Regulations were passed in 2015 by the UK Parliament and detailed guidelines were then drawn up and adopted by the regulator, the Human Fertilization and Embryology Authority (HFEA), who granted the first license to carry out the procedures to researchers in Newcastle in 2017. However, the techniques are now being used elsewhere, and not just to avoid mitochondrial disease, but as a way to overcome female infertility where preimplantation embryos generated by *in vitro* fertilization (IVF) repeatedly fail to develop. There is no established explanation for why MRTs should work for the latter women, and therefore application of these methods in such cases is speculative. The revised Guidelines therefore limit the clinical use of MRTs to those at high risk of transmitting serious mtDNA-based diseases to their offspring and when no other treatments are acceptable. Such use now falls under Category 2, whereas previously MRTs were in Category 3. Due to inadequate pre-clinical data and scientific rationale, the Guidelines also recommend not using MRTs for unexplained female infertility associated with poor oocyte/embryo quality. Notably, the Guidelines also encourage more research to refine and assess the safety and efficacy of MRTs, in particular to address a potential problem of "reversion," which was seen in preclinical data involving the culture of ES cells derived from MRT embryos, where the maternal mtDNA may come to predominate again (Greenfield et al., 2017)

Genetic alteration of the mitochondrial genome (mtDNA)

Genome editing of mtDNA provides another approach to allowing women at risk to have a genetically related child free from mitochondrial disease. This could be done in addition to the use of MRTs to eliminate the possibility of any carryover of the abnormal mtDNA by simply cutting and destroying the maternal mtDNA haplotype, or it could be carried out as an alternative, either to reduce the proportion of mutant mtDNA in cases of heteroplasmy or to correct the relevant sequence in the mtDNA. Research involving editing of mtDNA in human embryos would be permitted under Category 2, however, transferring them into a human uterus for gestation is currently not permitted. The latter is placed in Category 3A because there is scientific rationale behind this possible approach but as yet insufficient preclinical data regarding safety and efficacy; indeed, in countries with relevant legislation, this is currently illegal. Ideally, there would also need to be demonstrable public support to use the methods clinically in any jurisdiction contemplating clinical use of these methods, which would be a form of heritable genome editing, albeit of the mitochondrial and not nuclear genome.

Human genome editing

Heritable genome editing (or germline genome editing for reproductive purposes). This remains a prohibited research activity because currently the methods are neither sufficiently safe nor efficient. However, because there are defensible reasons for pursuing this line of research, this has been placed in Category 3A. These reasons may include situations where correcting a deleterious gene variant is the only way that prospective parents may have a genetically related child (see the commission report from the National Academy of Sciences, 2020). However, any decision to

proceed with clinical use of the methods will be dependent not only on substantial preclinical assessments as to safety, efficiency, and efficacy, but also on appropriate policies, regulation, and oversight being in place. It will also require meaningful public engagement, political support, and proper oversight within the relevant jurisdiction.

The commission report provides guidance for initial clinical uses of human germline genome editing once the technical, safety, and ethical issues are resolved, including a case-by-case evaluation of scientific methods and the societal and ethical issues associated with any proposed use. The revised ISSCR guidelines also encourage the development of a comprehensive regulatory and ethical framework for overseeing heritable human genome editing that builds on the existing regulatory frameworks for new biotechnologies, the practice of medicine, and describes a set of principles that should be followed. The report from the WHO's Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, which is due to be published in May 2021, provides a framework for governance, as well as other material that should be of benefit when considering not just heritable human genome editing, but also somatic genome editing (see below).

Non-heritable (non-reproductive) germline genome editing. It follows that preclinical research to optimize methodologies and minimize potential harms associated with any heritable application is encouraged. Such research, if it involves human embryos (either surplus embryos from IVF that are not wanted for reproduction and have been donated for research, or embryos that are created specifically for research), would be placed in Category 2 and subject to robust review and oversight, as would any basic research involving human genome editing to explore, for example, the role of specific genes during early embryogenesis. The use of other germline cells for this research, notably pluripotent stem cells and gamete progenitors, including spermatogonial stem cells, would fall under Category 1A or 1B, respectively, unless these were being used to create embryos, in which case it would move to Category 2.

Somatic genome editing. The Guidelines also provide new guidance on somatic genome editing research and applications, including *in utero* genome editing and stem cell-based interventions. Notably, clinical research involving *in utero* stem cell-based interventions or genome editing involves two patients, the pregnant woman and the future child, and should be undertaken, preferably in the context of a well-designed clinical trial, only when it offers the prospect of a benefit greater than that of post-natal interventions, does not pose excessive risk to the pregnant woman, and there is institutional capacity for autopsy (in the case of miscarriage or stillbirth) or follow-up (in the case of live birth).

Basic and preclinical research on somatic genome editing, which is conducted *in vitro* and/or in animal models, should not require specialized review and oversight and falls into Category 1A. Clinical research and applications of somatic genome editing should largely be covered by existing review and oversight mechanisms governing gene therapy (Doudna, 2020). However, detailed and additional considerations are provided within a new appendix to the ISSCR Guidelines. The WHO's Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing also considers somatic genome editing. It does so because, as well as offering potential treatments, applications of somatic genome editing could be open to abuse and malpractice, and the topic also raises issues of social and distributive justice. The WHO Committee's report should again provide an authorative reference point for considering governance in this area.

PROCUREMENT OF CELLS AND TISSUES/ DERIVATION OF STEM CELL LINES

The revised ISSCR Guidelines provide a new three-tiered system to streamline the review process for the procurement of banked and historical cell lines while maintaining a rigorous review process for the procurement of embryos and gametes for stem cell research. In each case, procurement should follow generally accepted principles of research ethics, including those related to donor consent, relevant laws, policies, and regulations in the jurisdiction, as well as the principles laid down in the Guidelines.

Tier 1: the procurement and use of banked and historical human cell lines is permissible if the materials have been deposited according to contemporaneous ethical and regulatory standards and are distributed consistent with the original consent given for their use, along with additional provisions spelled out in the Guidelines. Notably, the latter include that Tier 1 cell lines should not be used for reproductive purposes, e.g., to create embryos from *in vitro*-derived gametes.

Tier 2: the procurement of fresh human somatic cells and tissues for the purposes of stem cell research should be reviewed by existing review and oversight committees, bolstered by relevant stem cell expertise.

Tier 3: the procurement of human gametes and embryos that are destined for use in human embryo research and stem cell research must be reviewed through the specialized oversight process as outlined in the Guidelines. This should include monitoring of the practices of donor recruitment to ensure that the decision of women to donate their oocytes (or embryos) is free of undue inducement and exploitation.

The Guidelines also stress that any review and oversight process must ensure that vulnerable individuals and populations are not exploited. There must be no undue inducements or other unacceptable influences for the provision of human cells and tissues. In addition, the Guidelines recommend that cell and tissue donors should be able to choose whether they wish to receive incidental findings, such as the presence of a risk allele for a genetic disease or cancer, and that this should be clear in the consent process. Provenance of stem cell lines must be easily verifiable by access to relevant documents such as material transfer and licensing agreements and data demonstrating the identity of the cell line and uses allowed under the original informed consent (Isasi et al., 2019). However, due to advances in and increasing ubiquity of genomic sequencing, researchers are strongly encouraged to maintain confidentiality when sharing genomic data that has the potential to connect donors and family members with de-identified cells and tissues (Isasi et al., 2014; Knoppers et al., 2011).

Overall, the revised Guidelines provide more realistic recommendations on the derivation and banking of new lines that will protect donors, facilitate research by making it clearer what is permitted or not, and ease compliance for companies developing stem cell-based products.

CLINICAL TRANSLATION

The number of clinical trials and other interventions involving stem cells has increased significantly over the last 5 years, as have the number of inappropriate uses and exaggerated or false claims. Given the knowledge gained regarding what works well, what might not, and what is lacking, considerable effort was taken to modernize the recommendations for clinical translation and regulator approval in the revised Guidelines.

To facilitate bona fide treatments, the Guidelines now include a new recommendation on sex as a biological variable (although this must apply also to basic and preclinical research), support the use of accelerated approval pathways based on surrogate or intermediate endpoints, encourage robust post-market surveillance systems in jurisdictions with conditional approval pathways, and encourage health systems and payers to establish a process for evaluating the health benefits and economic value of stem cell-based interventions.

New or updated recommendations are also made in the Guidelines to curb premature or inappropriate commercialization of cell therapies; consequently they include an updated recommendation to forcefully caution against the premature commercialization of unproven stem cell-based interventions. They also adopt international standards for defining stem cell-based products as drugs or advanced therapy medicinal products (ATMPs) if such products have been substantially manipulated or are provided for non-homologous uses; this standard aligns with the US FDA, the EMA, and Australia's TGA). They include new recommendations on regulations authorizing stem cell-based products, including the demonstration of substantial evidence of effectiveness in appropriately powered, well-controlled clinical trials, with statistically significant findings. They narrow the types of stem cell-based products eligible for the medical innovation pathway that is aligned with international regulatory standards, including the US FDA. Finally, they strengthen the recommendation on patient registries to clarify their use as a tool for disease histories and tracking long-term patient outcomes. The recommendation also notes that registries are not adequate substitutes for randomized controlled trials to demonstrate the safety and efficacy of products for marketing authorizations. Indeed, in some cases the registries seem to be used merely as a form of advertising, a practice that is at best misleading and goes against a duty of care for patients.

CONCLUSIONS

It is hoped that these revised Guidelines are sufficiently forward looking to capture the science surrounding human stem cell and embryo research and its social and regulatory context, not just now, but also its likely trajectory over the next several years. It is notoriously difficult to predict how any of these might change and over what time scale. This has been evident over the last 5 years, with many advances and altered opinions necessitating an extensive set of revisions. Neither the field nor those involved in it should remain static; consequently, the Guidelines will need to evolve and should be read with this in mind. Nevertheless, the principles underlying the Guidelines, which have not changed from earlier versions, will endure. Therefore, whether carrying out research or treating patients, adhering to these principles should always be the priority.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.stemcr.2021.05.012.

DECLARATION OF INTERESTS

R.L.-B. has no financial conflicts to declare. R.L.-B. serves on the following advisory boards: Scientific and Clinical Advances Advisory Committee of the Human Fertility and Embryo Authority; Sense About Science, Member of Board of Trustees; Public Library of Science (PLOS), Board Member, Chair of Audit Committee, Chair of Remunerations Committee, and member of Scientific Advisory Board; Royal Society, Chair of "Genetic Technologies

Programme," Progress Educational Trust, Chair of the Board of Trustees; member of the WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing; Chair of ISSCR Task Force to Update the Guidelines; and member of External Advisory Board, "Cambridge Reproduction Strategic Research Initiative," University of Cambridge, UK.

R.B. receives funding from UK NIHR, MRC, Wellcome, Cure Parkinson's Trust, and EU. R.B. received funding from Parkinson's UK, CHDI, Rosetrees Trust, and Evelyn Trust. R.B. receives royalties from Wiley and Springer and also has an ongoing consultancy role for the following companies: Novo Nordisk, UCB, Aspen Neuroscience, and BlueRock Therapeutics.

A.H.B. is a co-founder of OvaNova, Inc., as well as a co-founder of Rumi Scientific, Inc.

R.A.C. is Professor Emerita, University of Wisconsin; David Hamburg Fellow, Nuclear Threat Initiative; and Lead Co-Chair, BioMADE. R.A.C is a member of the WHO Expert Advisory Group on Genome Editing; member of the Planning Committee, Third International Summit on Genome Editing; and Co-Chair of the US National Academy of Medicine committee on emerging science, technology, and innovation.

A.C. is a board member of the ISSCR and scientific advisory board member of the Tepper Foundation.

G.Q.D. holds patents relevant to stem cells and is a founder of and member of the scientific advisory board of 28/7 Therapeutics, Inc.

S.G. is also a part-time employee and stock-holder of Sana Biotechnology, a cell therapy company; he holds relevant patents and his lab receives sponsored research support from Sana.

A.G. is a current or recent board member of the following: the National Academies International Commission on Heritable Human Genome Editing; the UK HFEA's Scientific & Clinical Advances Advisory Committee; and the UK Nuffield Council on Bioethics until 2020. A.G.'s core funding is from the Mammalian Genetics Unit at MRC Harwell (MC_U142684167).

J.K. holds a patent on the cerebral organoid method and is co-founder and scientific advisory board member of a:head bio.

D.J.H.M. is a member of the Maryland Stem Cell Research Commission and a paid Academic Collaborator of the National Academy of Medicine's Committee on Emerging Science, Technology, and Innovation in health and medicine.

L.N. is an inventor on patents on lentiviral vector technology and targeted genome editing filed by Telethon Foundation and/or San Raffaele Scientific Institute. L.N. is a founder and/or owns equity and is a scientific advisory board member of Genenta Science, Magenta Therapeutics, Genespire, and Tessera.

R.P. is an advisor and has stock options in BIT BIO.

J.R. is a member, Board of Directors, Notch Therapeutics; member, Editorial Board, *Stem Cell Reports*; and member, Editorial Board, *Cell Stem Cell*.

N.R. is an inventor on two patents describing the blastoid technology (EP2986711 and EP21151455.9). N.R. has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation program ERC-Co grant agreement no. 101002317.

M.S. is affiliated with the following: Institute for the Advanced Study of Human Biology (WPI-ASHBi), Kyoto University, Yoshida-Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan; Department of Anatomy and Cell Biology, Graduate School of Medicine, Kyoto University, Yoshida-Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan; and Center for iPS Cell Research and Application (CiRA), Kyoto University, 53 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan. M.S. is an inventor on patent applications relating to the induction of germ cells from PSCs filed by Kyoto University.

J.S. is a member of Merck KGaA's Bioethics Advisory Panel and Stem Cell Research Oversight Committee; a member of IQVIA's Ethics Advisory Panel; a member of Aspen Neurosciences Scientific Advisory Board; a member of a Merck Data Monitoring Committee; a consultant to Biogen; and a consultant to Portola Pharmaceuticals, Inc.

L.T. has no financial interests to declare. L.T. is member of ISSCR's Ethics Committee and Membership Committee and was a member of one of the working groups involved in revising and updating ISSCR's guidance document.

The other authors declare no competing interests.

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